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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/607,571	BATYCKY ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/3/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *140-143, 146-150, 153, and 156-173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *140-143,146-150,153 and 156-173* is/are rejected.

7)☒ Claim(s) *171* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 140-143, 146-150, 153, and 156-173 are pending. Applicants previously cancelled claims 1-139, 145, 151-152, and 154-155. Applicants have newly cancelled claim 144. Receipt and consideration of Applicants' amended claim set and arguments/remarks submitted on September 3, 2008 are acknowledged. Any rejections previously of record that are not explicitly maintained herein have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 140-143, 153, and 156-160 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) **is maintained** for the reasons of record restated below.

Applicant Claims

Applicants claim a method for administering epinephrine to a patient in need of epinephrine comprising administering spray-dried particles from a dry powder inhaler to the respiratory system of a patient in a single, breath-activated step, the particles comprising (a) epinephrine or a salt thereof and, (b) at least one pharmaceutically acceptable excipient, wherein the particles administered to the patient comprise at least about 50 micrograms of epinephrine, have a tap density of less than 0.4 g/cm^3, and possess a fine particle fraction of less than 5.6 microns of at least about 45 percent.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Tarara discloses engineered particles that may be used for the **delivery of a bioactive agent to the respiratory tract of a patient**. The particles may be used in the form of dry powders or in the form of stabilized dispersions comprising a nonaqueous continuous phase. In particularly preferred embodiments the particles may be used **in conjunction with an inhalation** device such as a dry powder inhaler, metered dose inhaler or a nebulizer (abstract).

Tarara discloses that the disclosed powders may comprise the selected agent or bioactive agent, or agents as the sole structural component of the perforated microstructures. Conversely,

the perforated microstructures may comprise **one or more components** (i.e. **structural materials, surfactants, excipients**, etc.) in addition to the incorporated agent [0040].

Tarara discloses that his invented preparations provide highly flowable dry powders that can be efficiently aerosolized, uniformly delivered, and penetrate deeply in the lung or nasal passages [0050]. Any bioactive agents that may be formulated in the perforated microstructures are expressly held to be within the scope of pharmaceutical preparations taught by Tarara, including **bronchodilators and steroids** [0069]. Exemplary medicaments of biologically active agents suitable for used in Tarara's formulations include bronchodilators, such as **adrenaline** [0070]. Adrenaline and epinephrine are synonyms for the same compound.

In preferred embodiments, Tarara's compositions are comprised of microstructures formed by **spray drying** [0075]. The **mean aerodynamic diameter of the perforated microstructures is preferably less than about 5 microns, and in particularly preferred embodiments less than 2 microns**. These particle distributions will facilitate deep lung deposition of the bioactive agent whether administered using a dry powder inhaler (DPI), metered-dose inhaler (MDI), or nebulizer [0126]. Tarara defines fine particle fraction (FPF) as "the percentage of the total amount of active medicament delivered per actuation from the mouthpiece of a DPI, MDI or nebulizer onto plates 2-7 of an 8 stage Andersen cascade impactor." Tarara's formulations preferably have a **fine particle fraction of approximately 20% or more by weight of the perforated microstructures** (w/w), even more preferably **from about 30 to 70% w/w**. In selected embodiments the present invention will preferably comprise a **fine particle fraction of greater than about 30%, 40%, 50%, 60%, 70% or 80% by weight** [0127].

Tarara states that skilled artisans would appreciate that the perforated microstructures of his invention are useful in DPIs used in inhalation therapies [0131]. Currently, the range of dry powder that can be filled into a unit dose container is from 5 to 15 mg, corresponding to a drug **loading ranging from 25 to 500 micrograms per dose (i.e. actuation)** and bulk reservoir type DPIs can meter between 200 micrograms to 20 mg of powder per actuation [0132].

Tarara discloses that stabilized dispersions of his invented pharmaceutical formulations are particularly suitable for the pulmonary administration of bioactive agents (e.g. adrenaline), which may be used for the **localized or systemic administration of compounds** to any location of the body [0186].

Applicant's attention is drawn to Examples X-XII, wherein Tarara discloses the preparation of various pharmaceutical particles comprising active agents, surfactant, and lactose excipient (Example XI), having **a tap density less than 0.1 g/cm^3**. Surfactants are excipients as well. The Examiner would also like to draw the Applicant's attention to Figure 5 in which Tarara discloses the distribution of an exemplary particulate composition in an Anderson cascade impactor as delivered by a DPI and a MDI. It is well known in the art that the different stages of the Anderson cascade impactor correlate to the delivery of particles to different regions of the pulmonary system, with stages 6-7 corresponding to delivery of particles to the deep lung (i.e. alveolar region of the pulmonary system). See for example, Radhakrishnan (U.S. Patent No. 5,192,528), where the correlation of the different stages of the Anderson cascade impactor with different regions of the pulmonary system is described.

Slutsky teaches a breath activated inhaler, which may contain a single dose of a powdered medicament, which is intended to be inhaled by the patient in a single breath (title;

abstract; col. 4, lines 47-49; col. 6, lines 27-62; col. 8, lines 50-55 and 60-62; col. 9, lines 25-30; col. 10, line 48 through col. 13, line 42, especially col. 12, lines 38-59). Slutsky teaches an alternative breath-activated inhaler capable of delivering a large dose of powdered medicament in a single breath (col. 12, lines 38-59).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Tarara lacks the explicit teaching that powdered formulations are delivered in a single breath actuated step. This deficiency is cured by the teachings of Slutsky.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been *prima facie* obvious to a person of ordinary skill at the time of the instant invention to combine the teachings of Tarara and Slutsky, because Tarara teaches powdered pharmaceutical formulations for inhalation administration and Slutsky teaches breath-activated inhalers for the administration of powdered medicaments. It would also have been obvious to combine the teachings of Tarara and Slutsky, because as taught by Slutsky, use of Slutsky's invented inhaler would allow one to deliver a large dose in a single breath. An ordinary skilled artisan would have been motivated to utilize an inhaler capable of delivering a therapeutically effective dose in a single breath, because this would clearly improve patient compliance. Patient compliance would clearly be improved, because one would need fewer administrations to deliver a therapeutically effective dose contained in an inhaler. Regarding the amount of epinephrine delivered, Applicants' claims have no maximum limit on the amount of

epinephrine delivered, merely that at least 50 micrograms is delivered. The combination of Tarara's invented compositions with Slutsky's invented inhaler would reasonably be expected to deliver at least 50 micrograms of epinephrine, because one can modify the dosage of epinephrine present in an inhaler to ensure the delivery of a therapeutically effective amount of epinephrine and Slutsky's inhaler permits delivery of an entire dose in a single breath. Therefore, an ordinary skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 9/3/08 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing: (1) the rejection is allegedly improper because the Examiner has allegedly failed to consider Applicants' invention as a whole; (2) Applicants are allegedly claiming a highly efficient method for the inhalation administration of epinephrine; (3) Slutsky is allegedly improperly relied on for the teaching of a fine particle fraction; (4) there is allegedly no evidence in Tarara that would support the conclusion that Tarara's teachings teach or suggest the delivery of at least 50 micrograms of any drug; (5) Slutsky's teachings of alternative embodiments in which (i) more than one inhalation of smaller doses is contemplated or (ii) the inhaler resistance is increased to slow administration allegedly teaches away from Applicants' invention; and (6) Applicants' claimed methods are implied to exclude the treatment of glaucoma and are allegedly limited to people in need of emergency administration of epinephrine in a crisis.

The Examiner respectfully disagrees with Applicants' traversal arguments. Regarding (1), Applicants ***claimed invention*** has been considered as a whole and has been found obvious for the reasons of record restated above. Regarding (2) and (6), in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., (i) highly efficient method of delivering epinephrine, (ii) a method of administration that excludes people suffering from glaucoma, (iii) a method of administration limited to people in need of epinephrine in a crisis or emergency situation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). If Applicants desire that the claimed method is exclusive of the delivery of epinephrine to people suffering from glaucoma, Applicants are kindly encouraged to amend their claims appropriately. As currently written, Applicants' claims do not exclude any person or patient to whom the administration of epinephrine is reasonably considered a valid treatment regimen, such as in the treatment of glaucoma.

Regarding (3), Applicants are mistaken. Slutsky is not relied upon for the teaching of a fine particle fraction. The above rejection clearly states that Slutsky is relied upon for the teaching of administration in a single breath actuated step. Tarara clearly teaches the FPF required by Applicants' claims. See for example, paragraphs [0127] or Figure 5. Tarara also clearly teaches spray-dried dry powders having a particle size of less than 5.6 microns (see paragraphs, [0111], [0126], [0210], [0232], [0247], [0261], [0272], [0279], etc.) characterized by a density of less than about 0.4 g/cm^3 (See, for example Applicants have attacked Tarara's

example XXI and have implied that Tarara's Example XXI is so deficient as to render the entire reference worthless. This is not persuasive, because as Applicants have correctly noted one must consider the entirety of a reference. Applicants are correct that 77 micrograms/actuation given over 20 actuations does not equal the 300 micrograms specified in Tarara's Example XXI as having been loaded into the dry powder inhaler. Nonetheless, this deficiency does not knock out the other teachings of Tarara, which clearly point to powder compositions characterized by a density of less than 0.4 g/cc, a FPF of less than 5.6 microns of at least about 45%, or the identification of epinephrine as a suitable medicament for incorporation in Tarara's invented compositions.

Regarding (4), Applicants are once again mistaken. Tarara clearly contemplates the delivery of amounts of active agent in amounts of 50 micrograms or more. In fact, the state of the art at the time of Tarara was that it was conventional to load dry powder inhalers with composition dosage amounts ranging from 5-15 mg, corresponding to drug loadings between 25 micrograms and 500 micrograms per actuation [0132]. Clearly, Applicants must agree that an amount of 500 micrograms is more than 50 micrograms. Furthermore, because Applicants' range of active agent delivered substantially overlaps with the prior art range, it would require no more the routine optimization to vary the amount of drug delivered. Thus, if Applicants' claim to fame is the delivery of amounts of active agent in excess of 50 micrograms, this limitation is well known and was well within the skill of the ordinary artisan at the time of the instant invention.

Regarding (5), the fact that Slutsky teaches alternative embodiments does not constitute a teaching away, because Slutsky combined with Tarara does not discourage, discredit, or dissuade

the ordinary skilled artisan from delivery of a therapeutic dose in a single breath actuated step. The fact that Slutsky also contemplates situations, such as administration of nicotine, wherein multiple inhalations may be desirable does not mean that Slutsky discourages the ordinary skilled artisan to administer the complete therapeutic dose in a single inhalation. It is noted that Applicants additionally allege that the Examiner has not shown that the combination of Tarara and Slutsky have not been shown to teach the "critical elements" of Applicants claims (FPF, particle size, and particle density). Applicants are mistaken, as has been demonstrated supra. The instant rejection is deemed to remain proper and is maintained.

The rejection of claims 161-162 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and further in view of Physicians' Desk Reference (PDR, page 1236) (already of record) **is maintained** for the reasons of record restated below.

Applicant Claims

Applicants claim a method as described above in the instant office action wherein epinephrine is administered to a patient suffering from anaphylaxis, edema, bronchoconstriction, bronchospasm, and/or airway constriction.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above. The teachings of the PDR were set forth on page 7 of the

office action mailed on April 6, 2006 mailed and are restated herein below. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above.

The 2002 PDR teaches on page 1236 that **epinephrine is essential in the treatment of anaphylaxis** (1st sentence in the section entitled "Precautions"). It also teaches in the "Clinical Pharmacology" section that epinephrine acts to relieve vasodilation and increased vascular permeability. It also **relaxes the bronchial smooth muscles**, which alleviates wheezing and dyspnea. Other conditions alleviated by administration of epinephrine are pruritis, urticaria, and **angioedema** and it may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Tarara lacks the teaching of a method of treatment wherein epinephrine is administered to treat anaphylaxis, edema, bronchoconstriction, bronchospasm, and airway constriction. This deficiency is cured by the teachings of the PDR.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Tarara/Slutsky and the PDR, because Tarara teaches pharmaceutical preparations wherein the perforated microstructures may comprise adrenaline (i.e. epinephrine) active agent and the PDR describes known treatments which utilize

epinephrine to treat anaphylaxis, angioedema, and relax the bronchial smooth muscles. A skilled artisan would have been motivated to combine the prior art references, because the PDR is a well-known medical reference consulted by physicians and other medical professionals to determine which medicaments are appropriate to treat which conditions or disorders. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because Tarara teaches pharmaceutical compositions comprising adrenaline and the PDR teaches treatments in which the administration of adrenaline is appropriate, such as in the treatment of anaphylaxis, bronchoconstriction, bronchospasm, etc.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 9/3/08 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing that although the PDR establishes that it was well known to delivery epinephrine to treat anaphylaxis, bronchoconstriction, bronchospasm, airway constriction, and edema it is allegedly unobvious to administer epinephrine by inhalation per Applicants' claimed method and that the PDR does not cure the alleged deficiencies of the Tarara/Slutsky combination. The traversal arguments presented against the instant rejection are essentially identical to those arguments rebutted above in the previous rejection. The Office's rebuttal arguments are herein incorporated by reference. The rejection is maintained.

Claims 140-143, 146-150, 159, 160, and 162 under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 2003/0215512) in view of Tarara et al. (US 2005/0074498) and Slutsky (U.S. Patent No. 6,102,036) **is maintained** for the reasons of record, which are restated below for Applicants' convenience, and further articulated below.

Applicant Claims

Applicants claim a method as described above in the instant office action.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of Foster were set forth on pages 8-10 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

Foster teaches a composition that comprises a mixture of a pharmaceutically acceptable glassy matrix and at least one pharmacologically active material within the glassy matrix. It may be further mixed with a powdered, pharmaceutically acceptable carrier (abstract).

Foster teaches that the powdered composition will be composed of **particles** having a mass median diameter (MMD) of about 1-5 microns and a mass median aerodynamic diameter **(MMAD) of about 1-5 microns** [0051]. The active materials in the composition are active drug substances preferably used for administration via pulmonary inhalation. The unit dosage typically will be between 0.25 mg and 15 mg of total material in the dry powder, wherein the

active will comprise **about 0.05% to about 99.0% by weight** of the composition [0054]. In the dry state the drug or phase containing the active **may be either crystalline or amorphous in form** [0055]. Active small molecules for **systemic and local lung applications** for use in Foster's compositions include steroids and bronchodilators, including **adrenaline** [0056]. Systemic diseases treatable using Foster's compositions are taught in [0060] and pulmonary diseases, which are suitable targets for treatment include, chronic bronchitis, asthma, ARD, COPD, **bronchospasm**, and bronchial asthma [0061]. In addition to the glass former, the composition may contain other additives (i.e. excipients) [0064], including non-polar amino acids (e.g. **leucine**) [0068]. The glass former may be used alone or **in combination with additives, which may be crystalline or amorphous** [0064]. Suitable glass formers include organic carboxylic salts and the most preferable glass formers include **sodium tartrate, lactose, etc.** [0071] to [0072]. In Examples 15-16, Foster teaches exemplary formulations comprising a small molecule active (albuterol). The Tables in [0232] and [0234] obviously disclose a FPF in the column with the heading "% particle mass < 5 microns in size."

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Foster lacks the teaching of compositions having a tap density of less than 0.4 g/cm^3, which is cured by the teachings of Tarara. Foster lacks the teaching of administration in a single breath-activated step. This deficiency is cured by the teachings of Slutsky.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant application to combine the teachings of Foster and Tarara/Slutsky, because all inventors teach compositions suitable for inhalation pulmonary administration of active agents. A skilled artisan would have been motivated to combine the teachings of Foster and Tarara, because Tarara's compositions provide teachings of desirable physical characteristics of aerodynamically light particles especially suitable for inhalation administration. An ordinary skilled artisan cognizant of the teachings of Slutsky would be motivated to utilize Slutsky's breath-activated inhaler to improve patient compliance and facilitate delivery of a particulate pharmaceutical formulation in the fewest number of administrations. A skilled artisan would have had a reasonable expectation of success upon combination both Tarara and Foster teach adrenaline-containing (i.e. epinephrine) compositions designed for inhalation pulmonary administration. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 9/3/08 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing: (1) the instant rejection is allegedly improper, because Applicants believe no teachings regarding the claimed FPF have been cited or are provided by the cited prior art references; (2) the teachings of Foster and Tarara are incompatible and the Examiner has allegedly failed to articulate how one would combine the

cited teachings to obtain inhalable compositions suitable for use with Slutsky's inhaler; and (3) Slutsky allegedly teaches away from the claimed method.

The Examiner respectfully disagrees with Applicants traversal arguments. Regarding (1), Applicants are mistaken. Teachings of the cited prior art meeting the claimed FPF limitations have been cited for both Tarara and Foster. Applicants allege that the data in Foster's table in paragraph [0232] does not correspond to the claimed FPF. The claimed FPF is defined as the percentage of particles with a size of less than 5.6 microns and is required to be greater than about 45%. In Foster's Table, more than 45 % of Foster's delivered dose consists of particles with a particle size of less than 5 microns, thus meeting Applicants' claimed FPF limitation. Applicants also point out that the data in Foster's table were not generated using a breath-actuated device. Applicants imply that the FPF results of Foster's compositions when administered from a breath-actuated device would necessarily not meet the recited FPF. Absent objective evidence to the contrary Applicants arguments are not persuasive. It is also noted that contrary to Applicants' belief, Tarara also teaches compositions meeting the recited FPF limitation recited in the claimed methods, as has already been established above.

Regarding (2), Applicants' have speculated that the combination of the teachings of Foster and Tarara would yield particles having particles exhibiting incompatible morphologies for inhalation administration as required by the teachings of Foster and Tarara. Aside from speculative arguments, Applicants have provided no evidence supporting their assertions that the combination of the teachings of Foster and Tarara would yield particles having unsuitable morphologies. Absent objective evidence to the contrary, Attorney speculative arguments are not found persuasive.

Regarding (3), this argument has already been addressed above in the 1st rejection under § 103(a). The Office's rebuttal argument is herein incorporated by reference. The instant rejection is maintained.

The rejection of claims 163-170 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and further in view of Warren et al. (*Clin. Pharmacol. Ther.*, 1986, *40(6)*, 673-678) (already of record) **is maintained** for the reasons of record restated and further articulated below.

Applicant Claims

Applicants claim a method as described above in the instant office action.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of Warren were set forth on pages 11-12 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

Warren et al. teach that inhalation of 30 puffs of adrenaline (3 mg) from a pressurized aerosol resulted in peak blood plasma levels of adrenaline **(C_{max}) of 4.22 ± 1.93 nM after 1 minute (T_{max}) of administration.** They compared these results to adrenaline administered by a

subcutaneous injection, which resulted in peak blood plasma levels of adrenaline **(C_{max}) of 2.43 ± 0.47 nM after 10 minutes (T_{max}) of administration**. The blood plasma levels of adrenaline were used as a measure of the systemic absorption of adrenaline (abstract, Figures 1 and 3 on pages 674 and 675, respectively).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Tarara lacks the express teaching of Cmax and Tmax of different administration routes, specifically inhalation administration vs. non-intravenous injection.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

A person of ordinary skill in the art at the time of the instant invention would have been able to obtain information on Warren et al.'s studies showing that the administration of inhaled adrenaline would lead to a shorter time for adrenaline blood plasma levels to reach a maximum concentration as a predictor of what one would expect upon inhalation administration of Tarara's pharmaceutical formulations. A skilled artisan would have known that drug blood plasma levels are a measure of the systemic absorption of a pharmaceutical agent and that said agent would therefore be acting systemically. Based on Warren's data, a person of ordinary skill in the art at the time of the instant invention would have been motivated to administer epinephrine to a patient and would have had a reasonable expectation that said drug administered by inhalation would result in maximal adrenaline blood serum levels in a shorter period of time when compared to non-intravenous injection routes of administration. Therefore, the claimed

invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 9/3/08 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by reiterating the same arguments presented to traverse the parent rejection based on Tarara and Slutsky and to argue that Warren does not cure these alleged deficiencies. The Examiner respectfully disagrees with Applicants' traversal arguments against the Tarara/Slutsky combination and incorporates herein by reference the rebuttal arguments set forth above. The instant rejection is maintained for the reasons of record set forth herein above.

The rejection of claims 172-173 under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 2003/0215512) in view of Tarara et al. (US 2005/0074498) and Slutsky (U.S. Patent No. 6,102,036) as applied to claims 140-143, 146-150, 159, 160, and 162 above, in further view of the *Drug Information Handbook* (1993) ("DIH") **is maintained** for the reasons of record restated below.

Applicant Claims

Applicants claim a method as described above in the instant office action.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of the DIH were set forth on page 12 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

The use of epinephrine bitartrate would have been readily apparent to a skilled artisan, because it is one of the most common salts of epinephrine employed in pharmaceutical formulations (*Drug Information Handbook*, Lexi-Comp, Inc.: Cleveland, OH, 1993, pp 322-325).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Tarara lacks the express teaching of the teaching of a composition comprising epinephrine bitartrate.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Tarara/Foster with the DIH, because the DIH is a standard reference used in the pharmaceutical art and the other two prior art references teach pharmaceutical compositions comprising epinephrine. A skilled artisan would have been motivated to combine the teachings of the DIH with those of Tarara and Foster, because epinephrine is a known active agent and

epinephrine bitartrate is a common salt of said active used in commercially available pharmaceutical formulations. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because Tarara, Foster, and the DIH teach compositions wherein the active is epinephrine, and the bitartrate salt of adrenaline is commonly used in pharmaceutical formulations. Regarding the amount of active agent, Foster teaches an overlapping range for the amount (i.e. about 0.05% to about 99.0% by w/w). In addition, it would have been readily apparent to a skilled artisan per the teachings of Foster that the remainder of the composition would comprise glass-forming excipient (i.e. sodium tartrate) and other additives (e.g. leucine). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 9/3/08 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing that (1) the teachings of Foster

and Tarara do not provide a reasonable expectation of success of mixing epinephrine, leucine, and sodium tartrate in specific amounts to obtain a composition; (2) Foster and Tarara allegedly are deficient because these references do not disclose or suggest the desirability of obtaining Applicants' claimed compositions; (3) the mere fact that both Tarara and Foster teach particulate formulations, which may contain adrenaline is an insufficient motivation to combine references; (4) there is allegedly no guidance in the combined prior art teachings for particular amounts of any of the ingredients; and (5) the Examiner has not shown the epinephrine is a glass former.

The Examiner respectfully disagrees with Applicants' traversal arguments. Applicants' formulations comprise epinephrine in the form of a conventionally administered epinephrine salt (epinephrine bitartrate) that is well known in the art (DIH). It is also noted the epinephrine bitartrate is the salt of epinephrine commercially used when epinephrine is administered by oral inhalation (DIH, p 325). The disclosure of a broad range of active agent in Foster's compositions is an invitation to an ordinary skilled artisan to optimize the amount of a particular active agent to find the optimal amount of said active suitable for the artisan's intended use of said composition. Upon determination of the optimum amount of epinephrine in a particulate formulation it would have been well within the skill of the ordinary artisan to vary the amount of the other conventional additives needed to obtain a composition exhibiting desirable properties. It is also noted that regarding amounts of active agent that Applicants' specification does not define the meaning of the term about. Thus, even an amount of active agent of 5% w/w would reasonably read on about 11 % w/w active agent.

Regarding (1), Applicants arguments are unpersuasive, because there is no reason of record that an ordinary skilled artisan would not have an expectation of successfully mixing a

well known active agent (i.e. epinephrine bitartrate) in particulate form with other well known and conventional particulate excipients (i.e. sodium tartrate and leucine). Regarding the selection of sodium tartrate, it is noted that sodium salts of organic acids are taught as being preferred glass formers according to Foster [0071] and sodium tartrate is explicitly identified as one of eight preferred glass forming excipients [0072]. Thus, the selection of sodium tartrate does not occur from a vast list as alleged by Applicants. An ordinary skilled artisan would conclude that one could mix epinephrine bitartrate, sodium tartrate, and leucine, because all these components are taught by the prior art.

Regarding (2) and (4), Applicants have not demonstrated any particular criticality attributed to the particular claimed components mixed in the recited amounts. It is the Examiner's position that mixing epinephrine, taught as being suitable for the preparation of inhalable dry powders, with excipients taught in the prior art as also being suitable for the preparation of particulate compositions is well within the capability of the ordinary skilled artisan and would have a reasonable expectation of success, absent evidence to the contrary. Applicants have cited data from copending Application 10/392,333 (copending '333), corresponding to dry powder compositions comprising "large" amounts of leucine that allegedly demonstrate surprising results. Specifically, Applicants highlighted formulate D on page 63 of the specification of copending '333. However, this data cannot be relied upon, because it has not been presented in a proper 1.132 declaration and copending '333 has not been incorporated by reference in the specification of the instant application. Furthermore, formulation D in copending '333 is not commensurate in scope with Applicants' claimed formulations in claims 172-173, because formulation D lacks sodium tartrate and epinephrine. Formulation D in

copending '333 also comprises mannitol (a sugar alcohol), ipratropium bromide (an anticholinergic drug), and salmeterol xinafoate (a betamimetic). Due to these differences, one is unable to conclude that any properties observed in formulation D of copending '333 are solely due to the presence of 80% leucine.

Regarding (3), an ordinary skilled artisan would have been motivated to combine the teachings of Foster wit the teachings of Tarara to obtain superior aerosolizable dry powders. The combination of Foster and Tarara would yield dry powder compositions more resistant to moisture and active agent degradation. Furthermore, Tarara provides guidance on how to obtain particulate compositions with desirable aerodynamic properties. Thus, as set forth above there is a reasonable motivation to combine.

Regarding (5), Foster's teachings do not require that the active agent is a glass former. Rather, it is the glass forming excipient that forms the glass matrix in which the active agent is found. Thus, it is unnecessary to demonstrate that epinephrine forms a glass, because the lack of this showing does not render the teachings of the combined references inoperable. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claim Objections

Claim 171 is objected to as being dependent upon a rejected base claim. The prior art of record does not provide a suggestion or motivation to formulate sustained release compositions

having the recited aerodynamic properties. It is noted that Applicants' specification incorporates by reference information about formulating sustained release compositions, which invariably all require the addition of phospholipids.

Conclusion

Claims 140-143, 146-150, 153, 156-172, and 173 are rejected. Claim 171 is objected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.H.A.-A.

Patent Examiner

Technology Center 1600

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616